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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Edwards & Angell, LLP
Intellectual Property Practice Group
P.O. Box 55874
Boston, MA 02205

EXAMINER	
NGUYEN, QUANG	
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1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,574	ISNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-61,63-66,68-70 and 72-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-61, 63-66, 68-70 and 72-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/24/08 has been entered.

Claims 49-61, 63-66, 68-70, 72 and new claims 73-75 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 49-61, 63-66, 68-70 and 72-75 are still rejected under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Hammond et al. (US Patent 5,880,090; IDS). ***This is a modified rejection.***

It is noted that the teachings of Isner (WO 97/14307) and Isner (US 6,121,246) are identical. For simplification, only the teachings of Isner (WO 97/14307) will be discussed in details below. Isner (WO 97/14307) teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic protein includes aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxidesynthase or muteins or portions thereof (page 5, lines 10-22). Isner (WO 97/14307) also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of

driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). **Isner (WO 97/14307) further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin (page 11, lines 15-19)**. Isner (WO 97/14307) also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner (WO 97/14307) or Isner (US 6,121,246) does not specifically teach the administration of an effective amount of a GM-CSF or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, **even though the reference teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.**

At the effective filing date of the present application Hammond et al already taught that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37); and that

the endothelialization-promoting agent can be administered by any route of delivery, including intravenous delivery (col. 4, lines 24-35).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of either Isner (WO 97/14307) or Isner (US 6,121,246) by further administering to the treated mammal an effective amount of GM-CSF or an effective fragment thereof, including via an intravenous delivery, in light of the teachings of Hammond et al, and since either Isner (WO 97/14307) or Isner (US 6,121,246) also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is also an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the therapeutic outcome. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Isner (WO 97/14307) or Isner (US 6,121,246) and Hammond et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 6/24/08 (pages 6-14) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue basically that the Examiner is not considering the Isner reference as a whole, particularly the rejection does not take into consideration **an essential element of the teachings of Isner of administration of the angiogenic agent directly to the ischemic tissue**. When taken as a whole, modification of Isner to include systemic administration as taught by Hammond would change the principle of operation of Isner and therefore the references can not be combined and the methods claimed in the instant application can not be *prima facie* obvious in view of the cited references. Applicants also argue that systemic administration was clearly known at the time of the filing of the Isner reference, however, systemic administration of agents presumably was insufficient to provide the high and local concentration of angiogenic agents over time that was required for the treatment of ischemia; and **the invention**

described in the Isner reference was made to overcome limitation in the prior art regarding the limitation of treatment methods which require the repeated doses of angiogenic proteins by intracellular administration over a range of 10 to 14 days; and therefore the Isner reference must be understood as teaching away from systemic administration of angiogenic agents. Applicants further argue that it would not be obvious to combine Isner with a reference that teaches administration of proteins that are likely liable and would require repeated administration, and the one example of Hammond that teaches systemic administration of GM-CSF provides results which are inconclusive or dubious at best (example 3); and that this result is not predictable or it would not motivate one to modify the method of Isner by administration of systemic GM-CSF.

Firstly, it should be noted that apart from new dependent claims 73-75 other claims encompass a method for treating ischemic myocardial tissue of a mammal involving direct administration of both a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof and GM-CSF or an effective fragment thereof into the myocardial tissue. Additionally, the claims do not require a single and/or multiple administrations of any angiogenic factor in any form.

Secondly, the essential element of a method for inducing the formation of a new blood vessels in an ischemic muscle tissue, including ischemic myocardial muscle tissue, in a human host **comprises or includes** the step of directly injecting into said tissue of said human host an effective amount of a DNA sequence encoding an angiogenic protein (see Summary of the Invention and claims). **The modified method**

as a result of combining the teachings of Isner and Hammond as set forth above still contains this essential element of Isner, particularly to meet the limitation of step b) of the instant claims. **Nowhere in the Isner reference that teaches explicitly that encoded gene products (not in the form of a vector or DNA or RNA), such as the angiogenic protein nitric oxide synthase, must be administered directly to ischemic tissue and that they should not be administered systemically when they are used in combination with an angiogenic factor in the form of a plasmid or a viral vector or DNA to enhance the activity of targeted cells** (page 11, lines 11-19). It should be noted that an angiogenic factor in the form of a plasmid or a viral vector or DNA **must be directly administered to the target ischemic tissue in order to attain a desired therapeutic effect** due to the lack of in vivo vector targeting. However, **an angiogenic factor in the form of a protein and/or peptide is not necessarily required to be administered directly to the ischemic tissue in order to attain a desired therapeutic effect**. Isner states clearly "**Recent investigations have established the feasibility of using recombinant formulations of such angiogenic growth factors to expedite and/or augment collateral artery development in animal models of myocardial and hindlimb ischemia**" (page 8, first paragraph); and "**In addition, therapeutic angiogenesis has been achieved in the same or closely related models following administration of recombinant endothelial cell growth factor (ECGF) (Pu, et al., Circulation, 88:208-215 (1993)) and VEGF (Takeshita et al., Circulation, 90:228-234 (1994) supra). Previous studies, employing the animal model of chronic limb ischemia, demonstrated an efficacy of intra-muscular**

endothelial cell growth factor (ECGF) (Pu, et al., Circulation, 88:208-215 (1993)) or VEGF (Takeshita, et al., Circulation, 90:228-234 (1994) supra) administration" (page 8, second full paragraph). The cited statement in the Isner "In studies with recombinant angiogenic growth factors, intra-muscular administration of the growth factor was repeated over a range of 10 to 14 days. Thus, one major limitation of recombinant protein therapy is **its potential requirement** to maintain an optimally high and local concentration over time" (page 1, bottom of second paragraph) does not indicate or suggest in any shape or form that therapeutic angiogenesis would not be obtained via a systemic delivery of a recombinant angiogenic growth factor. Furthermore, it should also be noted that Isner teaches clearly that "If necessary, the nucleic acid may be reinjected to provide additional expression of the angiogenic protein" (page 5, lines 1-2). **This statement indicates clearly that the method of Isner can involve repeated doses or repeated injections to provide additional expression of an angiogenic protein**.

Thirdly, there is nothing unpredictable or dubious about the result shown in example 3 of the Hammond patent. Example 3 showed clearly that in the two dogs that received G-CSF, 80% and 35% of the graft surfaces were covered with ELC, and in the controls, 20-30%. Moreover, the teachings of Hammond et al. are not necessarily limited only to example 3, and the allowed claims of an issued US patent are considered to be valid until proven otherwise. The teachings of Hammond et al. clearly supported that **exemplified G-CSF and other agents (such as SCF, GM-CSF, see allowed claims) are capable of mobilizing bone marrow derived endothelial progenitors to**

promote endothelialization of vascular grafts *in vivo*. Furthermore, **the circulating CD34+ or Flk-1+ cells can participate in the repair of ischemic tissue as proposed by Asahara et al. as evidenced at least by the results reported in the article of Science 275:965-967, 1997 (This reference is specifically cited by Hammond et al.). The results showed that the EC progenitors can be incorporated into sites of active angiogenesis in animal models of ischemia**.

Fourthly, Isner teaches clearly that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells in a method for enhancing blood vessel formation or an angiogenesis in an ischemic tissue, including ischemic cardiomyopathy or myocardial ischemia, in a mammal. Hammond et al. teaches clearly that SCF, GM-CSF, G-CSF are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for enhancing the endothelialization of synthetic vascular grafts in a patient. **Hammond also notes that CD34+ circulating cells in blood can participate in the repair of ischemic tissue** (col. 3, lines 28-37). As already pointed out in the above rejection, an ordinary skilled artisan would have been motivated to modify the method of Isner by further administering to the treated mammal with an effective amount of at least one of SCF, GM-CSF and G-CSF, or an effective fragment thereof because Hammond already demonstrated that the aforementioned cytokines are capable of mobilizing bone-marrow derived endothelial cell progenitors in the blood, and that this mobilization of endothelial cell progenitors would further enhance blood vessel formation or angiogenesis in an

ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the angiogenic therapeutic outcome.

2. With respect to the Hammond reference, Applicants discussed in details examples 1-3 in the reference, even though examples 1-2 do not concern with GM-CSF or G-CSF. With respect to example 3, Applicants continue to question whether the reported data in the example is meaningful. With respect to the issue of CD34+ circulating cells in blood can participate in the repair of ischemic tissue, Applicants also argue that the data of Hammond only strongly suggest that CD34+ cells at best are participants, and the fact that a cell type can be used in a process does not mean that it is useful alone in the absence of appropriate co-factors. Applicants further argue that if any conclusion can be drawn from Hammond, one may conclude that the systemic administration of angiogenic agents does not consistently work and is a reason for the inconclusive, and therefore failed experiment. Additionally, Hammond could be seen as confirming the teachings of Isner that administration to the site of desired angiogenesis is essential by providing a high and local concentration of angiogenic agents and other growth factors, as would be provided by the bone marrow coated graft, angiogenesis is promoted.

Once again, there is nothing unpredictable or dubious about the result shown in example 3 of the Hammond patent. Example 3 showed clearly that in the two dogs that received G-CSF, 80% and 35% of the graft surfaces were covered with ELC, and in the controls, 20-30%. Moreover, the teachings of Hammond et al. are not necessarily limited only to example 3, and the allowed claims of an issued US patent are considered

to be valid until proven otherwise. The teachings of Hammond et al. clearly supported that **exemplified G-CSF and other agents (such as SCF, GM-CSF, see allowed claims) are capable of mobilizing bone marrow derived endothelial progenitors to promote endothelialization of vascular grafts *in vivo***. Furthermore, **the circulating CD34+ or Flk-1+ cells can participate in the repair of ischemic tissue as proposed by Asahara et al. as evidenced at least by the results reported in the article of Science 275:965-967, 1997 (This reference is specifically cited by Hammond et al.). The results showed that the EC progenitors can be incorporated into sites of active angiogenesis in animal models of ischemia**. Lastly, Hammond et al teach clearly that the endothelialization-promoting agent can be administered by any route of delivery, including **intravenous delivery** (col. 4, lines 24-35), not necessarily directly to a desired site such as the site of a synthetic vascular graft.

Accordingly, amended claims 49-61, 63-66, 68-70 and 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Hammond et al. (US Patent 5,880,090; IDS). for the reasons already set forth above.

Amended claims 49-61, 63-66, 68-70 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS). ***This is a modified rejection.***

It is noted that the teachings of Isner (WO 97/14307) and Isner (US 6,121,246) are identical. For simplification, only the teachings of Isner (WO 97/14307) will be discussed in details below. The teachings of Isner (WO 97/14307) have been presented above. However, Isner (WO 97/14307) or Isner (US 6,121,246) does not specifically teach the administration of an effective amount of a colony stimulating factor (CSF) or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, even though either one of the Isner references teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application Bussolino et al already demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see at least abstract; Methods; Table IV; page 994, col. 1, first paragraph; col. 2, first full paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of either Isner (WO 97/14307) or Isner (US 6,121,246) by utilizing recombinant G-CSF and/or GM-CSF as an endothelial cell mitogen to be administered to a patient in need thereof in light of the teachings of Bussolino et al, and since either one of the Isner references already teaches that **an angiogenic factor can be**

combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is also an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Bussolino et al. already demonstrated by exemplification that at least recombinant G-CSF has angiogenic activity *in vivo*, and that it also exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. This would in effect optimize the desired therapeutic outcome. The synergistic effects in the induction of angiogenesis would also be reasonably expected for the interaction between the administered G-CSF or GM-CSF and encoded bFGF or its fragment being expressed from a delivered nucleic acid. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Isner (WO 97/14307) or Isner (US 6,121,246) and Bussolino et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicants' arguments with respect the above rejection in the Amendment filed on 6/24/08 (pages 15-17) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Once again, Applicants argue that the essential element of the teaching of Isner of administration of the angiogenic agent directly to the ischemic tissue, and when taken as a whole, modification of Isner to include systemic administration would change the principle of operation of Isner.

Please refer to the examiner's responses to the same Applicant's arguments in the rejection of claims 49-61, 63-66, 68-70 and 72-74 under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Hammond et al. (US Patent 5,880,090; IDS) above.

2. With respect to the Bussolino reference, Applicants argue basically that Bussolino teaches that the observations were "surprising" and did not find his results predictable, and the data resulted in a "paradox" rather than an understanding and that more experiments need to be done as conclusions can not be drawn from the results in the reference. Accordingly, Bussolino does not provide a reasonable expectation as to how further experiments using his combination of growth factors and cytokines will result, never mind how other combinations will result; and that the Bussolino reference can not provide a motivation to modify another reference. Applicants further argue that the results of the corneal pellet assay of Bussolino provides a high and local concentration of G-CSF and bFGF in the pellets; and neither the Isner nor the Bussolino

reference provides any teaching or suggestion to administer one or more angiogenic agents systemically; and that both references teach that success from systemic administration is unlikely, at best.

Firstly, the examiner notes that Applicants mischaracterized the teachings of Bussolino et al. The results of Bussolino et al. **indicated clearly** that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, **recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis** (see at least abstract; Methods; Table IV; page 994, col. 1, first paragraph; col. 2, first full paragraph). Although angiogenic activity of G-CSF is weak relative to bFGF; **the combination of bFGF and G-CSF resulted in an angiogenic response *in vivo* that might be a co-operative interaction or a synergistic effect of these two cytokines**. Regardless of the nature of the interaction, an unexpected angiogenic response was obtained by combining non-angiogenic doses of bFGF and G-CSF *in vivo*. The co-operative effect of G-CSF and bFGF in inducing *in vivo* angiogenesis was **somewhat surprising and intriguing** because Bussolino et al found **no indication of a synergistic action of these two cytokines on HUVEC proliferation and migration *in vitro***; and Bussolino et al concluded that these observed results should be added to a list of factors or conditions **for which *in vitro* modulation of proliferation and migration is not necessarily predictive of in vivo effects on angiogenesis**. The statement "This initial observation needs to be

extended" does not refute the observed fact that **recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis**. The statement could imply that underlying biochemical mechanisms that are responsible for the *in vivo* synergistic effect between G-CSF and bFGF should be investigated.

Secondly, it should be noted **that the concept of using multiple growth factors to attain at least additional as well as synergistic effects (e.g., enhancing effects) for promoting cell proliferation and repair, including angiogenesis, is already established in the prior art** as evidenced at least by the teachings of Ferrara et al. (US 5,322,671; IDS). For example, Ferrara et al taught explicitly that VEGF can be combined with other novel or conventional therapies (e.g., growth factors such as aFGF, bFGF, PDGF, IGF, NGF, EGF, TGF-alpha) **for enhancing the activity of any of the growth factors** including VEGF, in promoting cell proliferation and repair (col. 16, lines 57-68).

Thirdly, it should be noted that apart from new dependent claims 73-75 other claims encompass a method for treating ischemic myocardial tissue of a mammal involving direct administration of both a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof and GM-CSF or an effective fragment thereof into the myocardial tissue. Additionally, new claims 73-75 were not rejected in this rejection.

Accordingly, amended claims 49-61, 63-66, 68-70 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US

6,121,246; IDS) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) for the reasons set forth above.

New claims 73-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) as applied to claims 49-61, 63-66, 68-70 and 72 above, and further in view of Pierce et al (US 6,689,351 with an effective filing date of at least 2/22/1991). ***This is a new ground of rejection.***

The teachings of either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Bussolino et al were already discussed above. However, none of the references teaches specifically that GM-CSF or an effective fragment thereof is administered systemically.

However, at the effective filing date of the present application Pierce et al. already taught at least that GM-CSF is administered parenterally, including intravenous administration, for therapeutic uses including for promoting accelerated wound healing in mammals (see at least col. 5, line 55 continues to line 27 of col. 6; Summary of the Invention, particularly col. 10, lines 7-8, lines 52-55; col. 12, lines 1-2).

It would have been obvious for an ordinary skilled artisan to further modify the modified method of either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) and Bussolino et al. by also administering GM-CSF systemically via at least intravenous administration into a mammal in need thereof in light of the teachings of Pierce et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Pierce et al already taught that that GM-CSF is routinely and successfully administered parenterally, including intravenous administration, for therapeutic uses including for promoting accelerated wound healing in mammals.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) with Bussolino et al. and Pierce et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49-61, 63-66, 68-70 and 72-75 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S.

Patent No. 6,121,246 in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) and Pierce et al (US 6,689,351). ***This is a new ground of rejection.***

The instant claims are directed to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) identifying a mammal which has, is suspected of having, or will have the ischemic tissue; b) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and c) administering to the mammal an effective amount granulocyte macrophage colony stimulating factor (GM-CSF) or an effective fragment thereof, thereby treating the ischemic myocardial tissue of the mammal.

Claims 1-15 of U.S. Patent No. 6,121,246 are drawn to a method for inducing the formation of new blood vessels in an ischemic tissue in a human host, **comprising**: a) selecting a human host in need of increased blood flow in an ischemic muscle tissue, and (b) directly injecting into said tissue of said human host an effective amount of a DNA sequence encoding an angiogenic protein or a modified angiogenic protein, wherein said DNA sequence comprises a promoter sequence and either a native secretory signal sequence or an operably linked secretory signal sequence, wherein the angiogenic protein or modified angiogenic protein is selected from the group consisting of acidic and basic fibroblast growth factors, vascular endothelial growth factor, endothelial cell growth factor, epidermal growth factor, transforming growth factor alpha and beta, platelet-derived endothelial growth factor, tumor necrosis factor alpha, hepatocyte growth factor, and insulin-like growth factor, and wherein said effective

amount of said DNA sequence expresses sufficient angiogenic protein in said tissue to induce new blood vessel formation in said human host.

The claims of the present application differ from the claims of the issued US patent 6,121,246 in reciting treating ischemic myocardial tissue of a mammal in need and further containing the additional step of administering to the mammal an effective amount of GM-CSF or an effective fragment thereof; with dependent claims 73-75 further recite the GM-CSF or an effective fragment thereof is administered systemically.

It is noted that the term "ischemic muscle tissue" in US patent 6,121, 246 encompasses ischemic cardiomyopathy and myocardial ischemia (col. 2, lines 54-61). Additionally, with respect to the open language of the term "comprising" in the claimed method of issued US patent 6,121,246; the patent discloses specifically that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase (an angiogenic protein) and others (col. 6, lines 4-14).

At the effective filing date of the present application, Bussolino et al already demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see abstract and Methods).

Additionally, Pierce et al. already taught at least that GM-CSF is administered parenterally, including intravenous administration, for therapeutic uses including for promoting accelerated wound healing in mammals (see at least col. 5, line 55 continues to line 27 of col. 6; Summary of the Invention, particularly col. 10, lines 7-8, lines 52-55; col. 12, lines 1-2).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the claims of the issued US patent 6,121,246 by further administering to a human host in need thereof, including a human host suffering myocardial ischemia, with an effective amount of GM-CSF or an effective amount thereof, including via a systemic delivery route such as intravenous administration in light of the teachings of Bussolino et al and Pierce et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Bussolino et al. already demonstrated by exemplification that at least recombinant G-CSF has angiogenic activity *in vivo*, and that it also exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. This would in effect optimize the desired therapeutic outcome. The synergistic effects in the induction of angiogenesis would also be reasonably expected for the interaction between the administered G-CSF or GM-CSF and encoded bFGF or its fragment being expressed from a delivered nucleic acid. Additionally, Pierce et al also taught that that GM-CSF is routinely and successfully administered parenterally, including intravenous administration, for therapeutic uses including for promoting

accelerated wound healing in mammals. Accordingly, the modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the issued claims in US patent 6,121,246, and the teachings of Bussolino et al. and Pierce et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Amended claims 49-59, 65 and 68-70 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 69-70 of copending Application No. 10/696,391 for the same reasons already set forth in the Office action mailed on 1/2/08 (pages 12-13). ***The same rejection is restated below.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment having the steps recited in either independent claim 69 or claim 70 in the copending Application No. 10/696,391 anticipates the claimed genus of a method for treating ischemic myocardial tissue of a mammal in need of such treatment in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub- should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Amended claims 49-61, 63-66, 68-70 and 72-75 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 52, 54-56, 58-65 and 68 of copending Application No. 10/696,391. ***This is a modified rejection.***

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are directed to a method for treating ischemic myocardial tissue of a mammal in need of such treatment comprising: a) identifying a mammal which has, is suspected of having, or will have the ischemic tissue; b) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and c) administering to the mammal an effective amount of a granulocyte macrophage colony GM-CSF or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal; whereas claims 49, 52, 54-56, 60-65 and 68 of copending Application No. 10/696,391 are drawn to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment comprising: a) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the

myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal, and (c) monitoring a cardiac function by the recited means, and wherein the method improves said cardiac function.

The claims of the present application differ from the claims of the copending Application No. 10/696,391 in reciting administering specifically to the mammal an effective amount of a granulocyte macrophage colony stimulating factor (GM-CSF) or an effective fragment thereof; and that GM-CSF or an effective fragment thereof is administered systemically. The claims of the present application can not be considered to be patentably distinct over claims 49, 52, 54-56, 58-65 and 68 of copending Application No. 10/696,391 when there is a specific disclosed embodiment of the co-pending application that teaches that SCF, CSF including GM-CSF or their fragments are the angiogenic factors; and that GM-CSF can be administered parenterally including intravenous, intra-arterial, intramuscular and interaperitoneal (page 19, first paragraph). Accordingly, the claims of the copending Application No. 10/696,391 fall within the scope of claims 49-61, 63-66, 68-70 and 72 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment in the co-pending application by also utilizing SCF and/or CSF, including GM-CSF or fragments thereof as angiogenic factors that support the instant claims. An ordinary skilled artisan would have been motivated to do this because these embodiments are explicitly disclosed in the co-pending application are preferred embodiments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that the above provisional double patenting rejections are not the only remaining rejections in the instant application.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633